NODAL inhibition promotes differentiation of pacemaker-like cardiomyocytes from human induced pluripotent stem cells.

Journal: Stem Cell Res

Publication Year: 2020

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PubMed link: 33128951

Funding Grants: Microenvironment for hiPSC-derived pacemaking cardiomyocytes

Public Summary:
Directed cardiomyogenesis from human induced pluripotent stem cells (hiPSCs) has been greatly improved in the last decade but directed differentiation to pacemaking cardiomyocytes (CMs) remains incompletely understood. In this study, we demonstrated that inhibition of NODAL signaling by a specific NODAL inhibitor (SB431542) in the cardiac mesoderm differentiation stage downregulated PITX2c, a transcription factor that is known to inhibit the formation of the sinoatrial node in the left atrium during cardiac development. The resulting hiPSC-CMs were smaller in cell size, expressed higher pro-pacemaking transcription factors, TBX3 and TBX18, and exhibited pacemaking-like electrophysiological characteristics compared to control hiPSC-CMs differentiated from established Wnt-based protocol. The pacemaker-like subtype increased up to 2.4-fold in hiPSC-CMs differentiated with the addition of SB431542 relative to the control. Hence, Nodal inhibition in the cardiac mesoderm stage promoted pacemaker-like CM differentiation from hiPSCs. Improving the yield of human pacemaker-like CMs is a critical first step in the development of functional human cell-based biopacemakers.

Scientific Abstract:
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